

REMARKS

Claims 17-49 are pending in the application. Claims 27, 38, and 49 have been amended to insert the word "either" to clarify that the "complement" recited in each claim refers to a complement of the probe, rather than a complement of the nucleotide. Claims 27, 38, and 49 have been amended to renumber the SEQ ID NO:s from 6, 7, and 8, to 1, 2, and 3, respectively. Claims 17-26, 28-37, and 39-48 have been cancelled. No new matter has been added.

The Examiner's statement that all species of claims 27, 38, and 49 are under examination is acknowledged.

Appendices A, B, and C (described below) are enclosed.

Priority

The Examiner alleged that Applicant is not entitled to claim priority from U.S. Application No. 09/658,659, filed September 8, 2000, and from U.S. Application No. 60/093,484, filed July 20, 1998 because these applications do "not disclose any basis of the single nucleotide polymorphisms of instant claims 27, 38, and 49."

The present application is a divisional of U.S. Application Serial No. 09/658,659, filed September 8, 2000, which is a CIP of Stanton, U.S. Application Serial No. 09/596,033, filed June 15, 2000, which is a CIP of Stanton, U.S. Application Serial No. 09/357,743, filed July 20, 1999, which is a CIP of Stanton, U.S. Application Serial No. 09/357,024, filed July 19, 1999, which claims the benefit of Stanton, U.S. Provisional Application 60/093,484, filed July 20, 1998.

Claim 27 is directed to a method comprising: (a) providing a sample comprising nucleic acid molecules present in a biological sample obtained from a patient; (b) contacting the sample with a probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:1, the probe comprising at least one of: (i) nucleotide 1066 wherein N is C; (ii) nucleotide 1136 wherein N is G; (iii) nucleotide 1497 wherein N is A; or the complement of the probe thereof; and (c) determining if the sample comprises a nucleic acid molecule that hybridizes to the probe.

SEQ ID NO:1 (formerly SEQ ID NO:6) corresponds to entry GEN-KL, thymidylate synthase, of Table 10, the sequence of which is also found under GenBank® Accession No. X02308. All of the variances recited in claim 27 are found in U.S. Application No. 09/658,659 in Table 10 on page 172, lines 29-32. The same variances are also found in U.S. Application No. 09/357,743 filed July 20, 1999, in Table 10, page 170, lines 40-44. **Therefore, all species of claim 27 are entitled to the priority of the application with the Serial Number 09/357,743, filed July 20, 1999.**

Claim 38 is directed to a method comprising: (a) providing a sample comprising nucleic acid molecules present in a biological sample obtained from a patient; (b) contacting the sample with a probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:2, the probe comprising at least one of: (i) nucleotide 276 wherein N is T; (ii) nucleotide 321 wherein N is C; (iii) nucleotide 452 wherein N is A; (iv) C is inserted after nucleotide 457; (v) nucleotide 491 wherein N is A; (vi) nucleotide 533 wherein N is C; (vii) nucleotide 624 wherein N is C; (viii) nucleotide 639 wherein N is G; (ix) nucleotide 655 wherein N is C; or the complement of the probe thereof; and (c) determining if the sample comprises a nucleic acid molecule that hybridizes to the probe.

SEQ ID NO:2 (formerly SEQ ID NO:7) corresponds to entry GEN-LUC, thymidylate synthase, of Table 10, the sequence of which is also found under GenBank® Accession No. D00517. All of the variances recited in claim 38 are found in U.S. Application No. 09/658,659 in Table 10, page 172, line 33 to page 173, line 6. The variances are also found in U.S. Application No. 09/596,033 in Table 10, page 177, lines 27-35. **Therefore, all species of claim 38 are entitled to the priority of the application with the Serial Number 09/596,033, filed June 15, 2000.**

Claim 49 is directed to a method comprising: (a) providing a sample comprising nucleic acid molecules present in a biological sample obtained from a patient; (b) contacting the sample with a probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:3, the probe comprising at least one of: (i) nucleotide 701 wherein N is C; (ii) nucleotide 716 wherein N is G; (iii) nucleotide 732 wherein N is C; (iv) nucleotide 1293 wherein N is G; (v) nucleotide 1322 wherein N is G; (vi) nucleotide 1379 wherein N is C; (vii) nucleotide 1590 wherein N is T; (viii) nucleotide 1688 wherein N is G; (ix) nucleotide 2401 wherein N is G; (x)

nucleotide 2429 wherein N is A; (xi) nucleotide 2488 wherein N is T; (xii) nucleotide 2594 wherein N is T; (xiii) nucleotide 2618 wherein N is A; (xiv) nucleotide 3083 wherein N is A; (xv) nucleotide 3125 wherein N is A; (xvi) nucleotide 3212 wherein N is T (xvii) nucleotide 3619 wherein N is A; (xviii) nucleotide 3635 wherein N is A; (xix) nucleotide 4256 wherein N is A; (xx) nucleotide 4898 wherein N is G; (xxi) nucleotide 5006 wherein N is T; (xxii) nucleotide 5062 wherein N is A; (xxiii) nucleotide 5167 wherein N is A; (xxiv) nucleotide 11069 wherein N is G; (xxv) nucleotide 11238 wherein N is T; (xxvi) nucleotide 11293 wherein N is G; (xxvii) nucleotide 11422 wherein N is C; (xxviii) nucleotide 11686 wherein N is T; (xxix) nucleotide 12598 wherein N is C; (xxx) nucleotide 13171 wherein N is C; (xxxi) nucleotide 13298 wherein N is A; (xxxii) nucleotide 13645 wherein N is C; (xxxiii) nucleotide 13751 wherein N is A; (xxxiv) nucleotide 13782 wherein N is C; (xxxv) nucleotide 13806 wherein N is C; (xxxvi) nucleotide 13813 wherein N is C; (xxxvii) nucleotide 14479 wherein N is G; (xxxviii) T is inserted after nucleotide 14546; (xxxix) nucleotide 14585 wherein N is T; (xl) nucleotide 14729 wherein N is A; (xli) nucleotide 14787 wherein N is T; (xlii) nucleotide 14795 wherein N is A; (xliii) nucleotide 15041 wherein N is C; (xliv) nucleotide 15343 wherein N is A; (xlv) nucleotide 15449 wherein N is A; (xlvi) nucleotide 15502 wherein N is A; (xlvii) nucleotide 15545 wherein N is T; (xlviii) nucleotide 15589 wherein N is G; (xlix) nucleotide 15769 wherein N is T; (l) nucleotide 15839 wherein N is G; (li) nucleotide 16148 wherein N is A; (lii) nucleotide 16198 wherein N is G; and (liii) nucleotide 16202 wherein N is T or the complement of the probe thereof; and (c) determining if the sample comprises a nucleic acid molecule that hybridizes to the probe. All of the variances recited in claim 49 are found in U.S. Application No. 09/658,659 in Table 10, page 173, line 7 through page 174, line 24. The following variances are also found in U.S. Application No. 09/596,033 in Table 10, page 177, line 36 through page 178, line 21: (i)-(viii), (xiv)-(xix), (xxxii-xl), (xli)-(xliii). Variance (l) is found in U.S. Application No. 09/596,033 in Table 11, page 180, line 12. **Therefore, variances (i)-(viii), (xiv)-(xix), (xxxii-xl), (xli)-(xliii) and (l) are entitled to the priority of the application with the Serial Number 09/596,033, filed June 15, 2000. The remaining variances of claim 49 are entitled to the priority of the application with the Serial Number 09/658,659, filed September 8, 2000.**

Copies of the pages of the prior applications containing the variances are enclosed. Appendix A contains a copy of Table 10, pages 169-171 of U.S. Serial No. 09/357,024.

Appendix B contains a copy of Tables 10 and 11, pages 171-180 of U.S. Application serial No. 09/596,033. Appendix C contains a copy of Table 10, pages 171-176 of U.S. Application Serial No. 09/658,659.

Claim Rejections Under 35 U.S.C. § 103

Claims 27, 38, and 49 are rejected under 35 U.S.C. § 103(b) over Billing-Medel et al. (U.S. Patent 6,130,043) in view of Dean (U.S. Patent 6,087,489). The Examiner stated that Billing-Medel et al. teaches a method comprising the steps of providing a sample comprising nucleic acid molecules present in a biological sample obtained from a patient, contacting the sample with a probe comprising at least 15 contiguous nucleotides of the nucleotide sequence; and determining if the sample comprises a nucleic acid molecule that hybridizes to the probe. The Examiner noted that "Billing-Medel et al. does not teach a probe comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:6 the probe comprising at least one of: (i) nucleotide 1066 wherein N is C; (ii) nucleotide 1136 wherein N is G; (iii) nucleotide 1497 wherein N is A; or the complements therefore...or nucleotide 452 wherein N is A in SEQ ID NO:7." The Examiner alleged that Dean et al. teaches a probe comprising these nucleotides. The Examiner stated

"it would have been prima facie obvious...to substitute and combine the probes comprising at least 15 contiguous nucleotides of the nucleotide sequence of SEQ ID NO:6, the probe comprising at least one of: (i) nucleotide 1066 wherein N is C; (ii) nucleotide 1136 wherein N is G; (iii) nucleotide 1497 wherein N is A; or the complements thereof, or nucleotide 452 wherein N is A in SEQ ID NO:7, or nucleotide 732 wherein N is C in SEQ ID NO:8, of Dean into the method of identifying a nucleic acid molecule which is the diagnostic marker of a disease of Billing-Medel et al...."

This rejection is respectfully traversed. Neither Dean et al. nor Billing-Medel et al. disclose any of the nucleotides variance of the present claims. SEQ ID NO: 1 of Dean et al. is identical to SEQ ID NO:1 (formerly SEQ ID NO:6) of the present application.

In one example, the Examiner cited SEQ ID NO:1 of Dean et al. because the nucleotide at position 1497 is a T in Dean et al. The Examiner indicated that the complement of A is T and that nucleotide 1497 of SEQ ID NO:1 of Dean et al. is T. Claim 27 of the present application, as amended, is directed to a probe comprising at least 15 contiguous nucleotides of the nucleotide

sequence of SEQ ID NO:1, the probe comprising...(iii) nucleotide 1497, wherein N is A; or the complement thereof. The word "either" has been added to clarify the fact that the "complement" refers to the complement of the probe sequence and not the complement of the nucleotide in isolation. A probe comprising nucleotide 1497 of SEQ ID NO:1 of the present application would contain an A at position 1497. The complement of the probe would contain a T at position 1497, but the surrounding sequence would also be the complement of SEQ ID NO:1. Dean et al. does not teach a probe comprising at A at position 1497 of SEQ ID NO:1, nor does Dean et al. teach a probe comprising a sequence complementary to a sequence of SEQ ID NO:1, wherein the nucleotide corresponding to position 1497 is a T. Dean et al. does not, therefore, render the claimed probe obvious.

In another example, the Examiner cited "nucleotide 452 wherein N is A in SEQ ID NO:7 (Abstract and SEQ ID NO:1, Column 29, line 1)" as evidence that Dean et al. teaches a probe that renders the claimed probes obvious. However, nucleotide 452 of SEQ ID NO:2 (formerly SEQ ID NO:7) of the present application refers to a nucleotide position within a genomic isolate of the thymidylate synthase gene. SEQ ID NO:2 is equivalent to GenBank® Accession Number D00517, which discloses exon 1 of the gene and genomic sequence surrounding exon 1. This position is not equivalent to position 452 of SEQ ID NO:1 of Dean et al., as SEQ ID NO:1 of Dean et al. corresponds to a cDNA sequence. Similarly, the Examiner's recitation of "nucleotide 732 wherein N is C in SEQ ID NO:8" as equivalent to "(Abstract and SEQ ID NO:1, Column 29, line 6)" is incorrect. Nucleotide 732 of SEQ ID NO:3 (formerly SEQ ID NO:8) corresponds to a position within a genomic sequence of thymidylate synthase.

Billing-Medel et al. contains no reference to thymidylate synthase, much less any variances within the thymidylate synthase gene. Therefore, Billing-Medel does not make up for the deficiencies of Dean et al.

Applicant asks that the rejection of the claims under 35 U.S.C. § 103(b) be withdrawn.



Table 10

Variance Table

Name	GID	OMIM_ID	VGX_Symbol	Description
Variance_Start	Variance	CDS_Context		

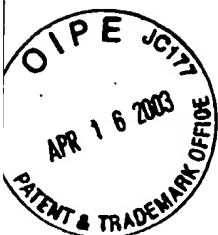
10	D13811D13811238310	GEN-AA	Glycine cleavage system: Protein T	
	277 148G>T	V50L		
	D13811D13811238310	GEN-AA	Glycine cleavage system: Protein T	
	1073 944G>A	R315K		
	D13811D13811238310	GEN-AA	Glycine cleavage system: Protein T	
	1083 954G>A	S		
	D13811D13811238310	GEN-AA	Glycine cleavage system: Protein T	
	1773 1644C>T	3		
15	D13811D13811238310	GEN-AA	Glycine cleavage system: Protein T	
	2037 1908C>T	3		
	J03626 J03626 258900	GEN-C6	Uridine monophosphate synthetase	
	(orotate phosphoribosyl transferase and orotidine-5-decarboxylase)	742 638G>C		
	G213A			
20	J03626 J03626 258900	GEN-C6	Uridine monophosphate synthetase	
	(orotate phosphoribosyl transferase and orotidine-5-decarboxylase)	1575 1471A>G		
	3			
	J03626 J03626 258900	GEN-C6	Uridine monophosphate synthetase	
	(orotate phosphoribosyl transferase and orotidine-5-decarboxylase)	1424 1320C>T		
25	S			
	J04031 J04031 None	GEN-CB	Methenyltetrahydrofolate cyclohydrolase	
	454 401G>A	R134K		
	J04031 J04031 None	GEN-CB	Methenyltetrahydrofolate cyclohydrolase	
	969 916C>G	Q306E		
30	J04031 J04031 None	GEN-CB	Methenyltetrahydrofolate cyclohydrolase	
	1614 1561T>C	S		
	J04031 J04031 None	GEN-CB	Methenyltetrahydrofolate cyclohydrolase	
	2011 1958G>A	R653Q		
	J04031 J04031 None	GEN-CB	Methenyltetrahydrofolate cyclohydrolase	
35	2335 2282C>T	T761M		
	K02581K02581188300	GEN-CI	Thymidine kinase 1	90 33C>T S
	K02581K02581188300	GEN-CI	Thymidine kinase 1	279 222G>A
	S			
	K02581K02581188300	GEN-CI	Thymidine kinase 1	282 225G>A
40	S			
	K02581K02581188300	GEN-CI	Thymidine kinase 1	772 715A>G
	3			
	K02581K02581188300	GEN-CI	Thymidine kinase 1	867 810G>A
	3			
45	K02581K02581188300	GEN-CI	Thymidine kinase 1	479 422C>T
	P141L			
	K02581K02581188300	GEN-CI	Thymidine kinase 1	112 55G>A
	G19R			
	K02581K02581188300	GEN-CI	Thymidine kinase 1	487 430G>A
50	E144K			
	K02581K02581188300	GEN-CI	Thymidine kinase 1	445 388A>G
	R130G			

	K02581K02581188300	GEN-CI	Thymidine kinase 1	313	256C>T
	F				
	K02581K02581188300	GEN-CI	Thymidine kinase 1	334	277G>T
	V93F				
5	K02581K02581188300	GEN-CI	Thymidine kinase 1	329	272-
	278TGGCTGT>TGGCTGT	S			
	M64590 M64590	238300	GEN-FU	Glycine cleavage system:	
	Protein P 3076 2926A>G	M976V			
	M69175 M69175	None	GEN-FX	Glycine cleavage system: Protein	
10	H 710 686C>G	3			
	M69175 M69175	None	GEN-FX	Glycine cleavage system: Protein	
	H 1007 983C>T	3			
	U09178U09178274270	GEN-HA	Dihydropyrimidine Dehydrogenase		
	166 85T>C C29R				
15	U09178U09178274270	GEN-HA	Dihydropyrimidine Dehydrogenase		
	577 496A>G	M166V			
	U09178U09178274270	GEN-HA	Dihydropyrimidine Dehydrogenase		
	3925 3844A>G	3			
	U09178U09178274270	GEN-HA	Dihydropyrimidine Dehydrogenase		
20	3937 3856T>C	3			
	U09178U09178274270	GEN-HA	Dihydropyrimidine Dehydrogenase		
	1708 1627A>G	I543V			
	U09178U09178274270	GEN-HA	Dihydropyrimidine Dehydrogenase		
	3432 3351T>C	3			
25	U09178U09178274270	GEN-HA	Dihydropyrimidine Dehydrogenase		
	3730 3649G>A	3			
	U09178U09178274270	GEN-HA	Dihydropyrimidine Dehydrogenase		
	638 557A>G	Y186C			
	U19720U19720600424	GEN-I1	Folate Transporter (SLC19A1)	341	246C>G
30	S				
	U19720U19720600424	GEN-I1	Folate Transporter (SLC19A1)	53	(-43)T>C
	5				
	U19720U19720600424	GEN-I1	Folate Transporter (SLC19A1)	175	80G>A
	R27H				
35	U19720U19720600424	GEN-I1	Folate Transporter (SLC19A1)	791	696C>T
	S				
	U50929U50929None	GEN-JF	Methionine synthetase (aka homocysteine		
	methyltransferase)	2017 1991A>G	3		
	U77088U77088None	GEN-K4	Thymidine kinase 2	1480	1472T>C 3
40	X02308X02308188350	GEN-KL	Thymidylate synthetase	1066	961T>C
	3				
	X02308X02308188350	GEN-KL	Thymidylate synthetase	1136	1031A>G
	3				
	X02308X02308188350	GEN-KL	Thymidylate synthetase	1497	1392T>A
45	3				
	X59543X59543None	GEN-M2	Ribonucleoside diphosphate reductase		
	850C>A	S			1037
	X59543X59543None	GEN-M2	Ribonucleoside diphosphate reductase		
	2223G>A	S			2410
50	X59543X59543None	GEN-M2	Ribonucleoside diphosphate reductase		
	2232A>G	S			2419
	X59543X59543None	GEN-M2	Ribonucleoside diphosphate reductase		
	2530T>A	3			2717

	X59618X59618180390	GEN-M3	Ribonucleotide reductase M2 polypeptide
	524 330C>G	S	
	X59618X59618180390	GEN-M3	Ribonucleotide reductase M2 polypeptide
	1636 1442C>T	3	
5	X59618X59618180390	GEN-M3	Ribonucleotide reductase M2 polypeptide
	2259 2065T>C	3	
	X59618X59618180390	GEN-M3	Ribonucleotide reductase M2 polypeptide
	189 (-6)T>G	5	
10	X90858X90858None	GEN-NQ	Uridine phosphorylase 1133 781T>A
	C261S		
	X17620X17620None	GEN-20M	Human mRNA for Nm23 protein, involved in developmental regulation (homolog. to Drosophila Awd protein)244 244G>T
	D82Y		
15	L38928L38928None	GEN-2PT	Homo sapiens 5,10-methenyltetrahydrofolate synthetase mRNA, complete cds 617 604A>G T202A
	S72487 S72487None	GEN-3LD	orf1 5 to PD-ECGF/TP...orf2 5 to PD-ECGF/TP [human, epidermoid carcinoma cell line A431, mRNA, 3 genes, 1718 nt]601 437G>C
	3		
20	M98045 M98045	None	GEN-4C3 Homo sapiens folylpolyglutamate synthetase mRNA, complete cds 1747 1677G>T 3
	M98045 M98045	None	GEN-4C3 Homo sapiens folylpolyglutamate synthetase mRNA, complete cds 1900 1830T>C 3
	L11931 L11931None	GEN-4DT	Human cytosolic serine hydroxymethyltransferase (SHMT) mRNA, complete cds 1444 1420C>T L474F
25	L11931 L11931None	GEN-4DT	Human cytosolic serine hydroxymethyltransferase (SHMT) mRNA, complete cds 1541 1517C>T 3
	DHFR J00140 126060	GEN-4E9	Human dihydrofolate reductase gene
	721 679T>A	3	
30	DHFR J00140 126060	GEN-4E9	Human dihydrofolate reductase gene
	829 787C>T	3	
	U09806U09806None	GEN-4FZ	Human methylenetetrahydrofolate reductase mRNA, partial cds 1289 1289C>A E430A
	U09806U09806None	GEN-4FZ	Human methylenetetrahydrofolate reductase mRNA, partial cds 473 473G>A R158Q
35	U09806U09806None	GEN-4FZ	Human methylenetetrahydrofolate reductase mRNA, partial cds 550 550C>T F
	U09806U09806None	GEN-4FZ	Human methylenetetrahydrofolate reductase mRNA, partial cds 668 668C>T A223V
40	U09806U09806None	GEN-4FZ	Human methylenetetrahydrofolate reductase mRNA, partial cds 1308 1308T>C 3
	U09806U09806None	GEN-4FZ	Human methylenetetrahydrofolate reductase mRNA, partial cds 120 120T>C S
45	U09806U09806None	GEN-4FZ	Human methylenetetrahydrofolate reductase mRNA, partial cds 1059 1059T>C S

Variance Table Table 10

5	Hugo	GID	OMIM	ID	VGX	Symbol	Description
	Variance	Start	Variance				CDS_Context
10	U73338	U73338	156570	GEN-69		Methionine Synthase	
	1136G	1252C	1334G	1699T	3150G	3207G	3209G 5444C 5551G 5573C 5659T 5678T 5874C 5934A
	1136G	1252C	1334G	1699T	3150G	3207G	3209G 5444C 5551G 5573C 5659T 5678T 5874C 5934A
	1136G	1252C	1334G	1699T	3150A	3207G	3209G 5444C 5551G 5573C 5659T 5678T 5874C 5934A
	1136G	1252C	1334G	1699T	3150A	3207G	3209G 5444C 5551G 5573C 5659T 5678T 5874C 5934A
	1136G	1252C	1334G	1699T	3150A	3207G	3209G 5444C 5551G 5573C 5659T 5678T 5874C 5934A
15	1136G	1252C	1334G	1699T	3150A	3207G	3209G 5444C 5551G 5573C 5659T 5678T 5874C 5934A
	1136		742G>A				V248M
	1158		764G>A				C255Y
	1252		858C>T				Silent
	1334		940G>A				D314N
20	1699		1305T>C				Silent
	3150		2756A>G				D919G
	3207		2813G>T				S938I
	3209		2815G>C				G939R
	5095		4701G>A				3'
	5444		5050C>A				3'
	5551		5157G>A				3'
	5573		5179C>T				3'
	5659		5265T>C				3'
	5678		5284T>C				3'
	5874		5480C>T				3'
	5934		5540A>G				3'
	6750		6356G>A				3'
25	D78011	D78011	222748	GEN-B0		Dihydropyrimidinase	
	129C	144G	670C	1131G	1158G		
	129T	144G	670C	1131G	1158C		
	129C	144G	670C	1131G	1158C		
	129C	144G	670T	1131G	1158C		
30	129		(-1)T>C				5'
	144		15G>A				Silent
	670		541C>T				R181W



[illegible]

40

	GEN-HA	Dihydropyrimidine Dehydrogenase
U09178	274270	
U09178		
166C	577A 3925A 3937C	
166C	577A 3925A 3937C	

166C 577A 3925A 3937C
166C 577A 3925A 3937T
166C 577A 3925G 3937C
166T 577A 3925G 3937C
166T 577A 3925A 3937C
166T 577G 3925G 3937C
166T 577A 3925A 3937T

166	85T>C	C29R
577	496A>G	M166V

20	1708	1627A>G	Y186C
	3432	3351T>C	I543V
	3730	3649G>A	3'
	3925	3844A>G	3'
	3937	3856T>C	3'

	U19720	U19720	600424	GEN-11	Folate Transporter (SLC19A1)
25	U19720	U19720	600424	GEN-11	Folate Transporter (SLC19A1)
	175G 341C 791C	1067G 1337C	1997T 2582T	2617C	2652T
	175G 341C 791T	1067G 1337C	1997T 2582G	2617T	2652T
	175G 341C 791C	1067A 1337C	1997T 2582T	2617C	2652T
	175A 341C 791T	1067G 1337C	1997C 2582G	2617T	2652T
	175A 341C 791T	1067G 1337C	1997T 2582G	2617T	2652T
30	175A 341C 791T	1067G 1337C	1997T 2582G	2617T	2652T

53	(-43)T>C	5'
175	80G>A	
341	246C>G	R27H
791	696C>T	Silent
1067	972G>A	Silent
1337	1242C>A	Silent
1997	1902T>C	3'
2100	2005~2006InsG	Frame
2582	2487T>G	3'
2617	2522C>T	3'

	2652	2557T>C	3'				
U77088	U77088	188250	GEN-K4	Thymidine kinase 2			
1480C							
1480T							
5	1480	1472T>C	3'				
X16396	X16396	None	GEN-LC	Methenyltetrahydrofolate dehydrogenase			
1397G	1480A						
1397A	1480A						
1397A	1480G						
1259		1244G>A	3'				
1397		1382A>G	3'				
1480		1465G>A	3'				
X59543	X59543	180410	GEN-M2	Ribonucleotide reductase M1 polypeptide			
1037A	2410G	2419A					
1037C	2410A	2419G					
1037C	2410A	2419A					
1037C	2410G	2419A					
1037A	2410A	2419A					
1037A	2410A	2419G					
20	1037	850C>A	Silent				
	1749	1562G>A	S521N				
	1846	1659C>T	Silent				
	2410	2223G>A	Silent				
	2419	2232A>G	Silent				
	2717	2530T>A	3'				
	2724	2537^2538insT	Frame				
	2882	2695A>C	3'				
X59618	X59618	180390	GEN-M3	Ribonucleotide reductase M2 polypeptide			
128G	189T	524C	1399T	1464G	1636C	1738C	2259T
128G	189G	524C	1399T	1464G	1636C	1738C	2259T
	128	(-67)G>A	5'				
	189	(-6)T>G	5'				
	524	330C>G	Silent				
	1399	1205T>A	3'				
	1464	1270G>A	3'				
	1636	1442C>T	3'				
	1738	1544C>T	3'				
	2259	2065T>C	3'				
X90858	X90858	191730	GEN-NQ	Uridine phosphorylase			
309C							
40							
35							
30							
25							
15							
10							

	309T	309	(-44)C>T	5'	
		824	472G>A	A158T	
5	X17620	X17620	156490	GEN-20M	Nucleoside Diphosphate Kinase A, partial
		244	244G>T	D82Y	
		488	488A>G	H163R	
	L38928	L38928	604197	GEN-2PT	Homo sapiens 5,10-methenyltetrahydrofolate synthetase mRNA,
	complete cds	617	604A>G	T202A	
	U55206	U55206	601509	GEN-35Z	Homo sapiens human gamma-glutamyl hydrolase (hGH) mRNA,
	complete cds	75T	150G	511C	703G
		75T	150G	511T	703A
		75T	150G	511C	703A
15		75T	150G	511C	703A
		75T	150G	511C	703A
		75			1161G
		150	16T>C	C6R	
		511	91G>A	A31T	
		703	452C>T	T151I	
			644A>G	N215S	
		1161	1102A>G	3'	
20	U81375	U81375	602193	GEN-3VO	Human placental equilibrative nucleoside transporter 1 (hENT1)
	mRNA, complete cds	1466G	1989G	1996C	2045T
		1466A	1989G	1996C	2045C
		1466G	1989G	1996T	2045C
		1466G	1989G	1996C	2045C
		1466			
		1989	1288G>A	A430T	
		1996	1811G>A	3'	
		2045	1818C>T	3'	
			1867T>C	3'	
	L11931	L11931	182144	GEN-4DT	Human cytosolic serine hydroxymethyltransferase (SHMT) mRNA,
	complete cds	1444C	1541T		
		1444T	1541C		
		1444T	1541T		
		1444C	1541C		
		1444			
		1523	1420C>T	L474F	
		1541	1499C>G	3'	
			1517C>T	3'	
40	U29200	U29200	None	GEN-4DU	Nucleoside diphosphate kinase B promoter

-

1977 1977G>A Genomic
2149 2149G>A Genomic
2467 2467A>G Genomic
2975 2975G>A Genomic
3116 3116G>T Genomic
3255 3255A>C Genomic
3344 3344T>C Genomic
4782 4782G>A Genomic
5022 5022T>C Genomic
5266 5266G>A Genomic
5285 5285C>G Genomic
5438 5438T>A Genomic
5482 5482C>T Genomic
5629 5629G>A Genomic
5648 5648C>T Genomic
5731 5731G>A Genomic

188350 GEN-LUC Thymidylate synthase, promoter

D00517 D00517 188350 GEN-LUC
276C 321T 452G 491C 533C 624A 639A
276T 321T 452G 491C 533C 624C 639A
276T 321C 452G 491C 533C 624C 639A
276C 321T 452G 491C 533T 624C 639A
276C 321C 452G 491C 533T 624A 639A
276T 321T 452G 491C 533C 624A 639A
276T 321C 452A 491C 533C 624C 639A
276C 321T 452G 491C 533T 624A 639A
276T 321T 452G 491A 533C 624C 639G

276 276C>T Genomic
321 321T>C Genomic
452 452G>A Genomic
457 457^insC Genomic
491 491C>A Genomic
533 533T>C Genomic
624 624A>C Genomic
639 639A>G Genomic
655 655T>C Genomic

D00596 D00596 188350 GEN-LUC Homo sapiens gene for thymidylate synthase, exons 1, 2, 3, 4,
5, 6, 7, complete cds
701 701A>C Genomic
716 716A>G Genomic
732 732T>C Genomic

1293 1293A>G Genomic
1322 1322C>G Genomic
1379 1379T>C Genomic
1590 1590C>T Genomic
1688 1688C>G Genomic
3083 3083G>A Genomic
3125 3125G>A Genomic
3212 3212C>T Genomic
3635 3635G>A Genomic
4256 4256G>A Genomic
13645 13645T>C Genomic
13751 13751C>A Genomic
13782 13782T>C Genomic
13806 13806T>C Genomic
13813 13813T>C Genomic
14479 14479A>G Genomic
14546 14546*Inst Genomic
14585 14585C>T Genomic
14729 14729G>A Genomic
14795 14795G>A Genomic
15041 15041T>C Genomic
U24253 136510 GEN-LUT Human folylpolyglutamate synthetase (FPGS) gene, exons 5-11,
and partial cds
1424A 1649G 2554A
1424C 1649G 2554G
1424C 1649A 2554A
1424C 1649G 2554A
1424
1649
2554
1424C>A Genomic
1649G>A Genomic
2554A>G Genomic
U24252 136510 GEN-LUT Polyglutamate synthetase, promoter and exons 1-4
266G 527C 1037G 1139G 1217C 1647C 1955G 2017G 2189A 2282C
266G 527C 1037G 1139G 1217C 1647C 1955A 2017G 2189A 2282C
266G 527C 1037G 1139G 1217C 1647T 1955A 2017G 2189A 2282C
266G 527C 1037A 1139G 1217C 1647C 1955A 2017G 2189A 2282C
266T 527C 1037G 1139G 1217C 1647C 1955A 2017G 2189A 2282C
266G 527C 1037A 1139G 1217C 1647C 1955A 2017G 2189A 2282C
266T 527C 1037G 1139G 1217C 1647C 1955G 2017G 2189A 2282C
266T 527C 1037G 1139G 1217T 1647C 1955A 2017G 2189A 2282C
266T 527C 1037G 1139G 1217C 1647C 1955A 2017A 2189A 2282C
266G 527C 1037G 1139G 1217C 1647C 1955A 2017A 2189A 2282C

266G 527C 1037G 1139G 1217C 1647C 1955A 2017G 2189G 2282C
 266G 527G 1037G 1139G 1217C 1647T 1955A 2017G 2189A 2282C
 266 266G>T Genomic
 527 527C>G Genomic
 1037 1037A>G Genomic
 1139 1139G>A Genomic
 1217 1217C>T Genomic
 1647 1647C>T Genomic
 1955 1955G>A Genomic
 2017 2017G>A Genomic
 2189 2189A>G Genomic
 2282 2282C>T Genomic
 AF061655 AF061655 123920 GEN-LUJ Cytidine deaminase, promoter
 575T 648T 771G 883G 1051A
 575T 648T 771G 883G 1051C
 575C 648T 771G 883A 1051A
 575C 648C 771C 883A 1051A
 575C 648T 771C 883G 1051A
 575C 648T 771C 883A 1051A
 575 575T>C Genomic
 648 648T>C Genomic
 771 771G>C Genomic
 883 883G>A Genomic
 941 941^insc Genomic
 1051 1051A>C Genomic
 K01612 K01612 None GEN-MT4 Dihydrofolate reductase, promoter
 1120C 1124G 1135G 1229G 1678C
 1120C 1124G 1135G 1229G 1678G
 1120T 1124G 1135G 1229G 1678C
 1120C 1124A 1135G 1229G 1678C
 1120 1120C>T Genomic
 1124 1124G>A Genomic
 1135 1135A>G Genomic
 1229 1229A>G Genomic
 1678 1678C>G Genomic

Variance Table

Table 11

Hugo Variance	GID Start	OMIM ID VGX Variance	Symbol CDS_Context	Description
5	D00596	188350	GEN-IUD	Homo sapiens gene for thymidylate synthase, exons 1, 2, 3, 4,
10	5, 6, 7, complete cds	235C>T	Genomic	
	6652	6652A>G	Genomic	
	15839	15839A>G	Genomic	
15	J03626	258900	GEN-C6	Uridine monophosphate synthetase (orotate phosphoribosyl
	transferase and orotidine-5'-decarboxylase)	638G>C	G213A	
	742	1320C>T	Silent	
	1424	172460	GEN-CB	Methenyltetrahydrofolate cyclohydrolase
	J04031	2956A>C	3'	
20	L38928	604197	GEN-2PT	Homo sapiens 5,10-methenyltetrahydrofolate synthetase mRNA,
	complete cds	604A>G	T202A	
	617	274270	GEN-HA	Dihydropyrimidine Dehydrogenase
	U09178	85T>C	C29R	
	166	703C>T	R235W	
	784	1601G>A	S534N	
25	1682	1627A>G	I543V	
	1708	2194G>A	V732I	
	2275	2657G>A	R886H	
	2738	2983G>T	V995F	
	3064	236250	GEN-4FZ	Human methylenetetrahydrofolate reductase mRNA, partial cds
30	U09806	668C>T	A223V	
	668	1289C>A	3'	
	1289	156570	GEN-69	Methionine Synthase
	U73338	6356G>A	3'	
	6750			

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Appendix C to reply for U.S. Application No. 09/963,333:
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Table 10

Variance Table

Hugo	GID	OMIM ID	VGX Symbol	Description	Variance Start	Variance	GEN-69	Methionine Synthase
10	194	(-201)C>G	5'		U73338	U73338	156570	GEN-69
	284	(-111)C>T	5'					
	1136	742G>A	VZ48M					
	1252	858C>T	Silent					
	1334	940G>A	D314N					
15	1699	1305T>C	Silent					
	3150	2756A>G	D919G					
	3207	2813G>T	S938I					
	3209	2815G>C	G939R					
	5444	5050C>A	3'					
20	5551	5157G>A	3'					
	5573	5179C>T	3'					
	5659	5265T>C	3'					
	5678	5284T>C	3'					
	5874	5480C>T	3'					
25	5934	5540A>G	3'					
	D78586	114010	GEN-BR	CAD PROTEIN				
	3434	3408C>T	Silent					
	4313	4287T>C	Silent					
	4799	4773A>G	Silent					
30	5255	5229C>T	Silent					
	5455	5429G>A	R1810Q					
	5507	5481T>C	Silent					
	5810	5784C>T	Silent					
	6128	6102C>T	Silent					
	6626	6600C>T	Silent					



	6686	6660C>T	Silent	
	U09178	U09178	274270	GEN-HA Dihydropyrimidine Dehydrogenase
	166	85T>C	C29R	
5	577	496A>G	M166V	
	638	557A>G	Y186C	
	1708	1627A>G	1543V	
	3432	3351T>C	3'	
	3682	3601C>T	3'	
	3730	3649G>A	3'	
	3925	3844A>G	3'	
10	3937	3856T>C	3'	
	U19720	U19720	600424	GEN-II Folate Transporter (SLC19A1)
	175	80G>A	R27H	
	341	246C>G	Silent	
15	791	696C>T	Silent	
	1067	972G>A	Silent	
	1337	1242C>A	Silent	
	1997	1902T>C	3'	
20	2100	2005~2006insG	3'	
	2582	2487T>G	3'	
	2617	2522C>T	3'	
	2652	2557T>C	3'	
	U92868	U92868	600424	GEN-LUK Homo sapiens reduced folate carrier (RFC1) gene, exons 1a, 1c and 1b
25	431	431A>G	Intron	
	441	441A>G	Intron	
	498	498C>T	Intron	
	579	579G>C	Intron	
	599	599G>C	Intron	
30	X02308	X02308	188350	GEN-KL Thymidylate synthetase
	1066	961T>C	3'	
	1136	1031A>G	3'	
	1497	1392T>A	3'	
	D00517	D00517	188350	GEN-LUC Thymidylate synthase, promoter
35	276	276C>T	Intron	
	321	321T>C	Intron	
	452	452G>A	Intron	

457	457TinsC	Intron
491	491C>A	Intron
533	533T>C	Intron
624	624A>C	Intron
639	639A>G	Intron
655	655T>C	Intron
D00596	D00596 188350	GEN-LUD
701	701A>C	Intron
716	716A>G	Intron
732	732T>C	Intron
1293	1293A>G	Intron
1322	1322C>G	Intron
1379	1379T>C	Intron
1590	1590C>T	Intron
1688	1688C>G	Intron
2401	2401A>G	Intron
2429	2429G>A	Intron
2488	2488C>T	Intron
2594	2594G>T	Intron
2618	2618G>A	Intron
3083	3083G>A	Intron
3125	3125G>A	Intron
3212	3212C>T	Intron
3619	3619T>A	Intron
3635	3635G>A	Intron
4256	4256G>A	Intron
4898	4898A>G	Intron
5006	5006C>T	Intron
5062	5062G>A	Intron
5167	5167G>A	Intron
11069	11069A>G	Intron
11238	11238C>T	Intron
11293	11293T>G	Intron
11422	11422T>C	Intron
11686	11686C>T	Intron
12598	12598T>C	Intron

13171 13171T>C Intron
13298 13298G>A Intron
13645 13645T>C Intron
13751 13751C>A Intron
13782 13782T>C Intron
13806 13806T>C Intron
13813 13813T>C Intron
14479 14479A>G Intron
14546 14546^{ins}T Intron
14585 14585C>T Intron
14729 14729G>A Intron
14787 14787C>T Intron
14795 14795G>A Intron
15041 15041T>C Intron
15343 15343G>A Intron
15449 15449G>A Intron
15502 15502G>A Intron
15545 15545C>T Intron
15589 15589A>G Intron
15769 15769C>T 3'
15839 15839A>G 3'
16148 16148G>A 3'
16198 16198T>G 3'
16202 16202G>T Intron
25 X59618 X59618 180390 GEN-M3 Ribonucleotide reductase M2 polypeptide
128 (-67)G>A 5'
189 (-67)T>G 5'
524 330C>G Silent
1399 1205T>A 3'
1464 1270G>A 3'
1636 1442C>T 3'
1738 1544C>T 3'
2259 2065T>C 3'
S72487 S72487 131222 GEN-3LD Thymidine phosphorylase, partial
183 19G>A D7N
483 319C>T 3'

5
10
15
20
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35

	601	437G>C	3'	
	1299	1135G>A	3'	
	M58602	131222	GEN-LUB	Thymidine phosphorylase, promoter and genomic
5	124	124C>T	3'	
	439	439G>A	3'	
	1044	1044TinsCT	3'	
	1331	1331G>A	3'	
	1977	1977G>A	Intron	
	2149	2149G>A	Intron	
	2467	2467A>G	Intron	
10	2634	2634C>G	Intron	
	2975	2975G>A	Intron	
	3116	3116G>T	Intron	
	3255	3255A>C	Intron	
	3344	3344T>C	Intron	
15	4051	4051C>A	Intron	
	4782	4782G>A	Intron	
	5022	5022T>C	Intron	
	5266	5266G>A	Intron	
	5285	5285C>G	Intron	
	5438	5438T>A	Intron	
	5482	5482C>T	Intron	
	5629	5629G>A	Intron	
	5648	5648C>T	Intron	
20	5731	5731G>A	Intron	
25	M98045	M98045	136510	GEN-4C3 Homo sapiens folypolyglutamate synthetase mRNA, complete cds
	802	732C>T	Silent	
	1747	1677G>T	3'	
	1900	1830T>C	3'	
30	U24253	U24253	136510	GEN-LUE Human folypolyglutamate synthetase (FPGS) gene, exons 5-11, and partial cds
	1424	1424C>A	Intron	
	1649	1649G>A	Intron	
	2554	2554A>G	Intron	
35	U24252	U24252	136510	GEN-LUF Folypolyglutamate synthetase, promoter and exons 1-4
	263	263A>G	Intron	
	266	266G>T	Intron	

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527 527C>G Intron
 1037 1037A>G 5'
 1139 1139G>A Intron
 1217 1217C>T Intron
 1647 1647C>T Intron
 1955 1955G>A Intron
 2017 2017G>A Intron
 2037 2037G>A Intron
 2189 2189A>G Intron
 2282 2282C>T Intron
 2309 2309A>G Intron
 U09806 U09806 236250 GEN-4FZ Human methylenetetrahydrofolate reductase mRNA, partial cds
 120 120T>C Silent
 464 464T>G M155R
 519 519C>T Silent
 668 668C>T A223V
 1059 1059T>C Silent
 1289 1289C>A 3'
 1308 1308T>C 3'
 1784 1784G>A 3'
 AF061655 AF061655 123920 GEN-LIJ Cytidine deaminase, promoter
 575 575T>C Intron
 648 648T>C Intron
 771 771G>C Intron
 883 883G>A Intron
 941 941T>insC 5'
 1051 1051A>C K27Q